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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/593,316	06/13/2000	John Clark	730/002	5627

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GERON CORPORATION
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/593,316	CLARK ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13-17 and 27-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Amendment filed March 19, 2002 has been entered and assigned as Paper #11. Claims 8-12, 18-21, and 23-26 have been canceled. Claims 33-37 are newly added. Claims 1-7, 13-17, and 27-37 are pending in the application, claims 1-6 and 33-37 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 1-6 stand rejected under 35 U.S.C. 112, first paragraph and the rejection applies to new claims 33-37, for the reasons of record advanced on Paper #7 and the following.

Applicants summarized issues raised in Paper #7 to a list of four points, and addressed the issues for written description and enablement together. Although the issue 2 is incorrectly characterized, a response to each of the issues appears below.

With respect to issue 1, whether heterozygous animals will have antibody-detectable Gal α (1,3)Gal determinants on their tissues, applicants argue that the specification indicates on page 36, line 25, that the expression of the epitope is autosomal dominant. Even though the text in page 36, line 25 discusses cell culture

maintenance, unrelated to the genotype and phenotype, the heterozygous animals will have antibody-detectable Gal α (1,3)Gal determinants on their tissues for an autosomal dominant epitope. Applicants seem to agree with the fact stating "a cell or animal that is inactivated for α1,3GT on just one allele will still have Gal α (1,3)Gal determinants on their cells at a density that would often still be antibody detectable, nevertheless, cells that have a knockout of only one locus are useful" (2nd paragraph in page 4). However, the point is not whether heterozygous knockout animals are useful, the point is whether the tissue and cells obtained from the fetus of the FD sheep is indeed devoid of Gal α (1,3)Gal determinants.

The specification teaches that by targeting Exon 4 of α1,3GT gene, two bands were observed from PCR analysis of umbilical cord of a sheep fetus, one band corresponding to the wild type α1,3GT gene, and another appropriate for a α1,3GT gene on one haplotype. This result indicates taht the fetus is heterozygous for inactivation of the α1,3GT gene (figure 17 and example 6). Therefore, the specification fails to teach whether a fetus or a mature ovine is obtainable in the event of a homozygous knockout of the α1,3GT allele, and it fails to show whether Gal α (1,3)Gal determinants is indeed undetectable in cells of the fetus from the fetus of the FD sheep. Such showing is necessary because in the event of a heterozygous knockout, Gal α (1,3)Gal determinants are not devoid in the organ and tissue; and in the event of a homozygous knockout, whether the fetus could tolerate the effect of the gene knockout and be brought to term is unpredictable. The specification only teaches the possession of a fetus of the FD sheep, in which α1,3GT gene is inactivated on one haplotype, it fails

to teach a live and matured sheep that is homozygous for inactivation of an α1,3GT gene, and it fails to teach any ovine tissue that is devoid of Gal α (1,3)Gal determinants. Therefore, from the disclosure of the specification, the skilled artisan could not recognize that applicants were in possession of the invention commensurate with the scope of the claims.

With respect to issue 2, the issue is not whether all tissue types falling within the scope of the claim is devoid of Gal α (1,3)Gal determinants, rather, it is whether, at the time of the effective filing date, applicants had in possession of the claimed ovine tissue devoid of antibody-detectable Gal α (1,3)Gal determinants, and which are made by any method, known or unknown, and it is about how the inactivation of α1,3GT is achieved. As cited in Paper #7 and reiterated here, *Edge* teaches (US 6,284,245) that Gal α (1,3)Gal epitope can be removed from the surface of a cell by a number of methods. The epitope can be cleaved from a cell surface by treatment of the cell with a α-galactosidase, by inhibiting α (1,3)GT activity, by antisense to α1,3GT gene, by treating cell with a chemical inhibitor of the enzyme, by a binding molecule to the epitope, etc. (2nd paragraph in column 6). *Hayashi et al* (Transplant Proc 1997;29:893) teach using adenoviral vector encoding antisense ribozyme to α1,3GT gene to inhibit α1,3GT gene expression to suppress hyperacute rejection to organ graft. *Sandrin et al* (US 5,821,117) claims a particular way of inactivating a porcine cell α1,3GT gene. However, the only ovine cell that meets the written description requirement, if they are proven to be homozygous knock out of α1,3GT allele, is made by disruption of Exon 4 of α1,3,GT gene. Therefore, from the disclosure of the specification, the skilled artisan could not

recognize that applicants were in possession of the invention commensurate with the scope of the claims.

With respect to issues 3, what the effect will be of the backgrounds of different strains of ovine, applicants argue that Linder reference targeting genes of endocrine molecules which mediate a complex response pathway between different cells, whereas the present invention is directed at inactivating a gene that puts a terminal sugar residue onto the carbohydrate substrate N-acetyl lactosamine, which all ovine animals express. The argument is not persuasive because the Linder reference teaches the influence of genetic factor to a phenotype, not physiological pathways, i.e. THE PRESENCE OF GENETIC MODIFIERS (ALLELIC VARIANTS AT LOCI OTHER THAN THE ONE BEING GENETICALLY MODIFIED) IN THE INBRED STRAIN GENOME. The claimed ovine animals are not even limited to inbred strains, the amount and effects of genetic modifiers to the gene targeted and to the phenotype caused by the gene targeting are highly unpredictable. Therefore, from the disclosure of the specification, the skilled artisan could not recognize that applicants were in possession of the invention commensurate with the scope of the claims.

With respect to issue 4, whether homologous recombination will work with strains of ovine that are different from Finn Dorset. The issue will be addressed in the next section.

For the reasons of record and those set forth above, the instant specification fails to meet the written description requirement for the broad scope.

ENABLEMENT REQUIREMENT

Claims 1-6 and 33-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inactivating an α1,3GT gene on one haplotype of the fetus of a FD sheep with a rAAV vector comprising a genetic construct disrupting Exon 4 of the α1,3GT gene, does not reasonably provide enablement for such inactivation in a mature ovine animal; the specification does not reasonably provide enablement for homozygous inactivation of α1,3GT gene in a fetus or a mature ovine animal by any means of inactivation; and it does not reasonably provide enablement for making ovine cells and tissue devoid of antibody-detectable Gal α (1,3)Gal determinants by homozygous or heterozygous inactivation of α1,3GT, in any strain of ovine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argued that use of non-isogenic DNA within the same strain may reduce the frequency but not the feasibility of homologous recombination, cited Riele et al, Mocikat et al and Zhou et al to support the argument, and concluded that it is reasonable to expect that homologous recombination using non-isogenic ovine vectors with or without reduction in recombination frequency, or using the method provided by the specification to construct proper targeting vectors. Applicants further pointed out that the last paragraph of Example 4 indicates that a particular vector targeting Exon 8 or 9 of the α1,3,GT gene in black welsh mountain fibroblasts did not cause homologous recombination to the extent tested, but a p0054 vector targeting Exon 4 was used successfully to create α 1,3,GT knockout cells.

The arguments have been carefully considered but found not persuasive for the reasons of record and the following.

As stated in Paper #7 and reiterated here, although the technique of making transgenic and knock out animals has become routine in the relevant art, the resulting genotype and phenotype varies significantly depending on the genes being manipulated, and the animals being used. In the instant case, the issues are whether the homologous recombination would occur, as well as what would be the resulting phenotype and whether a particular targeting site is suitable for producing the desired animal with the right phenotype. In fact, applicants experience further support the teaching of *Linder* to indicate such unpredictability. Apparently, the successful inactivation of the α1,3GT gene on one haplotype occurred in the fetus of both BWM and FN strains with a vector comprising the construct disrupting Exon 4 of the gene, but not Exon 8 or Exon 9. Further, the specification fails to teach whether the fetus could be brought to term even in FD strain after a heterozygous or homozygous inactivation of the α1,3GT gene. Thus, the phenotype resulting from homozygous and heterozygous targeted disruption of α1,3GT gene in different ovine strains would expect to be varied and unpredictable, particularly in view that the scope of the claims embrace a broad class of mature ovine animals and ovine cells that are heterozygous or homozygous for inactivation of α1,3GT gene by any means, and devoid of antibody-detectable Gal α (1,3)Gal determinants, or of detectable α1,3GT expression.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *homozygous inactivation of* α1,3GT gene in an ovine

animal, in particular for obtaining ovine tissue devoid of antibody-detectable Gal α (1,3)Gal determinants, the lack of guidance provided by the specification as well as the absence of working examples with regard to homozygous inactivation of α1,3GT gene in an ovine animal, and the breadth of the claims directed to the use of numerous means to abolishing Gal α (1,3)Gal determinants in any ovine animal, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
May 15, 2002

JAMES KETTER
PRIMARY EXAMINER